Appendix D

Categorical Regression Analysis

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Categorical Regression Analysis

Guth and associates (1991) described an alternative quantitative method to estimate a chemical concentration associated with a low probability of observable adverse effects. The method uses categorical regression analysis of the probability of a group of exposed subjects demonstrating a statistically significant adverse effect relative to control subjects. The adverse effects are divided into three severity categories: No Observed Adverse Effect Level (NOAEL), Adverse Effect Level (AEL), and Frank Effect Level (FEL); AEL and FEL categories are combined for the analysis. Experimental observations from various species may be depicted on the same plot to determine whether certain species are more sensitive than others to the toxicological effects of exposure to a particular chemical. The form of the modeled concentration-duration-response relationship is:

$$Ln(p/1-p) = \alpha + \beta_1 * Ln(C) + \beta_2 * T$$

where p is the probability of observing an AEL or FEL
α is the intercept parameter
β_1 and β_2 are slope parameters
C is the exposure concentration
T is the exposure duration.

A data set for a given experimental concentration and duration associated with a p=0.1 for an AEL/FEL response is estimated to be associated with a 10% probability of being categorized as an AEL/FEL data set and a 90% probability of being categorized as a NOAEL data set. This method of analysis takes into account the experimental duration and concentration, eliminating the need to perform any further time extrapolation (i.e., with the formula $C^n * T = K$) as is done with the NOAEL and BD methods.

While this method has not been formally adopted by OEHHA or USEPA, it has potential applications that may make it the preferred one under some circumstances. This method allows the information from a large number of smaller studies reporting NOAEL or LOAEL data to be combined and therefore strengthens the conclusions reached.

Figure D-1 depicts a plot of the categorical regression of acute human and rat central nervous system effects resulting from exposure to a hypothetical chemical. Data are presented on a log concentration vs. linear duration axis. Each separate dose group in each study is depicted by a single point. An acute toxicity exposure level for this chemical could be derived from the dose at which exposures are predicted to result in a probability of 0.1 that an AEL would be observed (the EC_{10}).

Appendix E

Glossary of Acronyms

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ACGIH	American Conference of Governmental Industrial Hygienists
AIHA	American Industrial Hygiene Association
ARB	Air Resources Board
BC	Benchmark Concentration
BD	Benchmark Dose
BC_{01}	Benchmark Concentration estimating at most a 1% response
BC_{05}	Benchmark Concentration estimating at most a 5% response
CAPCOA	California Air Pollution Control Officers Association
CAAQS	California Ambient Air Quality Standard
CARB	State of California Air Resources Board
CEPRC	California Emergency Planning and Response Commission
CNS	Central Nervous System
EC_{10}	Dose at which an adverse effect would be observed with a probability of 0.1
EEGL	Emergency Exposure Guidance Level
ERPG	Emergency Response Planning Guideline
FEL	Frank Effect Level
IDLH	Immediately Dangerous to Life or Health Level
LC_{50}	Air concentration lethal to 50% of the test population
LCL	Lower Confidence Limit
LD_{50}	Oral dose lethal to 50% of the test population
LOAEL	Lowest Observed Adverse Effect Level
MF	Modifying Factor
MLE	Maximum Likelihood Estimate
NAS	National Academy of Sciences
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NRC	National Research Council
OEHHA	Office of Environmental Health Hazard Assessment
RADS	Reactive Airways Dysfunction Syndrome; acute, irritant induced asthma
RD_{50}	Concentration resulting in a 50% reduction in respiratory rate
REL	Reference Exposure Level
SPEGL	Short-term Public Emergency Guidance Level
TC_{05}, TC(05)	Increase in toxic response by 5%
TLV	Threshold Limit Value
TWA	Time Weighted Average
UF	Uncertainty Factor
USEPA	United States Environmental Protection Agency

For definitions of chemical acronyms, please refer to individual acute toxicity summaries.

Appendix F

Modified LOAEL to NOAEL Uncertainty Factor

Appendix F

The following was presented at the 1997 Society of Toxicology Meetings by GV Alexeeff, J Fowles, D Dodge, M Hill.

Modified LOAEL to NOAEL Uncertainty Factor

I. Introduction

Many of the acute Reference Exposure Levels in this document are based on no-observed-adverse-effect-levels (NOAELs) for appropriate endpoints in key studies. NOAELs have been defined by U.S. EPA as the exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its control (U.S. EPA, 1994).

Due to the absence of a NOAEL in some key studies, some of the exposure levels are based on a lowest-observed-adverse-effect-level (LOAEL). The threshold is defined as the dose or exposure below which a significant adverse effect is not reported; thus, it is thought to be between the NOAEL and the LOAEL. To estimate a NOAEL when one is not available, the LOAEL is commonly divided by an uncertainty factor (UF) between 1 and 10, based on the severity of the adverse effect of the LOAEL (Dourson and Stara, 1983). In practice, 10 has generally been used as the UF for standard setting and is considered a health-protective value for adjusting a LOAEL to a NOAEL. An uncertainty factor of 3 has on occasion been used to arrive at the NOAEL, particularly for less severe non-lethal endpoints such as mild irritation. The justification for use of a UF between 1 and 10 is generally based on chronic or subchronic LOAEL to NOAEL ratios (Dourson and Stara, 1983); guidance specifically for acute toxicity is unavailable. Specific justification for the use of a UF for the LOAEL to NOAEL extrapolation is lacking for acute toxicity.

The purpose of this Appendix (Alexeeff *et al*., 1997) is to evaluate the distribution of the LOAEL to NOAEL ratios for acute inhalation studies and to consider the importance of severity of the adverse effect in the evaluation. This may provide a more objective scientific basis for the determination of UFs in LOAEL to NOAEL extrapolations.

II. Method of Analysis

The analysis evaluated 210 acute inhalation studies of 66 chemicals for which there were 873 LOAEL/NOAEL ratios. The LOAEL and NOAEL values were divided into three levels of increasing toxicity:

1. Discomfort or mild adverse effect level. These effects include irritation of eyes, nose and throat. Most LOAELs and NOAELs in this group were based on controlled human exposures.

2. Disabling or severe effect level. These effects include severe or long-lasting injury and developmental or reproductive effects. Most LOAELs and NOAELs in this category originated from animal studies.

3. Life threatening or lethal effect level. All LOAELs and NOAELs in this category were based on animal lethality data.

For the LOAEL/NOAEL ratio analysis, the Univariate procedure option of the SAS version 6.08 (1990) was used. Within severity level comparisons included: (1) lowest LOAEL divided by its appropriate NOAEL; (2) all LOAELs divided by their appropriate NOAELs; (3) all LOAELs (without 100% responses) divided by their appropriate NOAELs; and (4) LC_{50} divided by its appropriate NOAEL (life-threatening data only). Across severity level comparisons included: (1) lowest severe LOAEL divided by mild NOAEL; (2) lowest life-threatening LOAEL divided by severe NOAEL; and (3) lowest life-threatening LOAEL divided by mild NOAEL

III. Results

Within Severity Level Comparisons (Tables 1-3):

At the 90th percentile, the results indicate a UF of 3.5 to 6 when calculating a NOAEL from a LOAEL within each severity category. At the 95th percentile, the results indicate a UF of 6 to 10 when calculating a NOAEL from a LOAEL within each severity category. The lethal NOAEL/LOAEL ratio was smaller than the NOAEL/LOAEL ratio for severe disability or for mild adverse effects.

Across Severity Level Comparisons (Table 4):

At the 90th percentile, the results indicate a UF of 10 to 12 when calculating a NOAEL for severe disability from a lethal LOAEL, or a NOAEL for mild discomfort from a LOAEL for severe disability. At the 95th percentile, the results indicate a UF of 10 when calculating a NOAEL for severe disability from a lethal LOAEL. When calculating a NOAEL for mild discomfort from a LOAEL for severe disability, the UF increases to 40.

IV. Conclusions

- The UF ratios of LOAELs to NOAELs across all adverse effects range from 2.2 within mild effects (50^{th} percentile) to 117 for life-threatening effects (99^{th} percentile). Choice of a UF of 10 to estimate a NOAEL from a LOAEL of a specified severity represents a 99^{th} percentile.

- To estimate a NOAEL from a LOAEL within the same severity level, the UF value appears to be independent of severity level. The notion that extrapolation to NOAELs for mild effects (i.e., irritation) requires a UF substantially less than extrapolations to NOAELs for lethality is not supported by the data reported.

- For each of the three acute toxicity levels, there was little difference in the LOAEL/NOAEL ratio for different estimates of the LOAEL. Thus, the results are robust and statistically sound.

- At the 90th percentile, the results indicate that the LOAEL to NOAEL UF is between the most common UFs used currently, 3 and 10. At the 95th percentile, 10 is the most appropriate value.

- The small LC_{50}/NOAEL ratios relative to other NOAEL/LOAEL ratios for lethality appeared to result from the higher quality study design of this subset of studies.

- In estimating a NOAEL for all acute inhalation adverse effects from a lethal LOAEL, a UF of 40 would be needed to avoid overestimating the NOAEL 95 % of the time.

Table 1. Comparison of LOAEL to NOAEL Ratios for Mild Adverse Effects

	n	50th %ile	90th %ile	95th %ile	99th %ile
Lowest LOAEL/NOAEL	112	2.2	5.0	6.2	10.0
All LOAELs/NOAEL	130	2.7	6.0	10.0	10.0
LOAELs (w/out 100% responses)/NOAEL	122	2.3	5.0	7.3	10.0

Table 2. Comparison of LOAEL to NOAEL Ratios for Severe Effects

	n	50th %ile	90th %ile	95th %ile	99th %ile
Lowest LOAEL/ NOAEL	92	2.0	5.0	10.0	11.2
All LOAELs/NOAEL	112	2.1	5.0	10.0	10.0
LOAELs (w/out 100% responses)/ NOAEL	89	2.3	5.0	10.0	11.2

Table 3. Comparison of LOAEL to NOAEL Ratios for Lethality

	n	50th %ile	90th %ile	95th %ile	99th %ile
Lowest LOAEL / NOAEL	260	1.5	3.5	6.6	10.0
All LOAELs / NOAEL	631	1.9	4.0	6.6	10.5
LOAELs (without 100% responses) / NOAEL	493	1.7	3.4	6.0	10.0
LC_{50} / NOAEL	88	1.7	2.9	3.5	6.4

Table 4. Estimating a Level of No-Adverse-Effects from a Lethal Level

	n	50th %ile	90th %ile	95th %ile	99th %ile
Lowest severe LOAEL / mild NOAEL	28	3.6	12	40	70
Lowest lethal LOAEL / severe NOAEL	31	3.9	10.0	10.0	18.7
Calculated Lowest Lethal LOAEL / mild NOAEL	--	7	24	40	117

V. References

Alexeeff GV, Fowles JR, Hill M, Dodge D. Stochastic evaluation of acute inhalation thresholds from reported LOAELs. [abstract #851]. Toxicologist 1997;36(1 pt 2):167.

Dourson ML, Stara JF. Regulatory history and experimental support of uncertainty (safety) factors. Regul Toxicol Pharmacol 1983;3:224-238.

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